

# Microalbuminuria Is Common in Japanese Type 2 Diabetic Patients

A nationwide survey from the Japan Diabetes Clinical Data Management Study Group (JDDM 10)

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ON BEHALF OF THE JAPAN DIABETES  
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Previous studies have reported a marked variation in the prevalence of microalbuminuria in type 2 diabetic patients ranging from 7 to 47% (1–13). The variation could arise from ethnic/genetic differences in susceptibility (3–11) and from methodological issues for investigating the prevalence, such as small-sized populations (3,12,13); single clinic–based studies (8,12); use of the dipstick method instead of quantitative determinations (4,5); or only a single measurement of urinary albumin excretion (UAE) (3–13), whereas multiple measurements have been recommended for years (14). In terms of investigating the prevalence of microalbuminuria in type 2 diabetic patients, we performed this study with the aim of investigating patients with a specific ethnicity (i.e., Japanese). The study had a large-sized population, a nationwide multicenter-based design, and a high proportion of data availability for clinical variables and for multiple measurements of UAE.

## RESEARCH DESIGN AND METHODS

A cross-sectional study was conducted that included 29 medical clinics (i.e., general practitioners) or general/university-affiliated hospitals from different areas in Japan, using the same software to incorporate patient records, as a working study group. Known as the Ja-

pan Diabetes Clinical Data Management Study Group (15), this group consists of medical doctors who volunteered to dedicate daily standard clinical work to scientific analysis. The study was performed in primary care settings. All consecutive patients with type 2 diabetes who visited each clinic/hospital from January 2004–July 2005 and whose diabetes was diagnosed before 2003 were included ( $n = 14,919$ ). Treatment goals recommended by the Japan Diabetes Society were A1C <6.5%, blood pressure <130/80 mmHg, and serum concentrations of total cholesterol <5.2 mmol/l, triglycerides <1.68 mmol/l, and HDL cholesterol >1.03 mmol/l (16). Type 2 diabetes was diagnosed according to the Japan Diabetes Society criteria (17). Quantitative measurement of urinary albumin-to-creatinine ratio (ACR) at least once a year has been recommended (14,16). Eligible patients were those with at least one measurement of ACR if without proteinuria and/or serum creatinine if with persistent proteinuria. Those with nondiabetic kidney disease or elevated serum creatinine without proteinuria were excluded ( $n = 75$ ). Those with no measurement of ACR without proteinuria were not included ( $n = 5,947$ ). Thus, 8,897 patients were appropriate for the study.

Nephropathy was staged as follows (16). Stage I: ACR <30 mg/g creatinine;

stage II: ACR  $\geq 30$  and <300 mg/g creatinine (i.e., microalbuminuria); stage III: ACR >300 mg/g creatinine and/or persistent proteinuria with serum concentration of creatinine <176  $\mu\text{mol/l}$  (2.0 mg/dl); stage IV: serum concentration of creatinine  $\geq 176 \mu\text{mol/l}$  with proteinuria; and stage V: being treated with dialysis. Nonfasting blood samples were obtained for measurements of A1C and serum concentrations of creatinine and lipids. The albumin concentration of random spot urine was determined by turbidimetric immunoassay and the creatinine by the enzymatic method. The geometric mean of two or three measurements of ACR was used. A1C was measured by high-performance liquid chromatography (normal range 4.3–5.8%). Results are given as means  $\pm$  SD. Comparison of clinical variables among the groups was performed by one-way ANOVA.  $P$  values <5% were considered to be significant.

**RESULTS** — Prevalence of microalbuminuria and clinical nephropathy was 31.6 (95% CI 30.6–32.6) and 10.5% (95% CI 9.9–11.1), respectively, categorized by ACR (60% multiple and 37% single determination) and serum creatinine (Table 1). Data availability was nearly 100%. Patients without measurement of ACR had similar clinical features; the mean age was 64 years, the distribution according to sex was 60/40% (men/women), BMI 24.0 kg/m<sup>2</sup>, duration of diabetes 12 years, A1C 7.1%, systemic blood pressure 132/77 mmHg, and glomerular filtration rate 66.9 ml/min per 1.73 m<sup>2</sup> (2). The fraction of patients on angiotensin receptor blocker (ARB) and/or ACE inhibitor was similar to that on calcium channel blocker, and the fraction of those on diuretics was low but increased at stages III and IV. The proportion of patients who achieved the treatment goal was 31% for A1C, 42% for blood pressure, and >50% for lipids.

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**Abbreviations:** ABR, angiotensin receptor blocker; ACR, albumin-to-creatinine ratio; UAE, urinary albumin excretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Clinical characteristics of subjects

	Total	Stage I	Stage II	Stage III	Stage IV	Stage V	P	Data availability
n (%)	8,897	5,152 (58)	2,812 (32)	657 (7)	242 (2.6)	34 (0.4)		
Age (years)	63 ± 11	61 ± 11	64 ± 11	67 ± 12	69 ± 11	63 ± 12	<0.0001	100
Male	66	66	63	72	70	82	<0.0001	100
BMI (kg/m <sup>2</sup> )	24.3 ± 3.8	24.1 ± 3.7	24.7 ± 4.0	25.1 ± 4.1	23.8 ± 3.9	23.9 ± 4.0	<0.0001	100
Count of ACR measurements (3/2/1/0)	3,209/2,006/3,167/239 (37/23/37/3)	2,091/1,308/1,753/0 (41/25/34/0)	950/627/1,235/0 (34/22/44/0)	168/71/179/239 (26/11/27/36)				
Duration (years)	12 ± 9	11 ± 8	12 ± 8	15 ± 10	17 ± 11	17 ± 11	<0.0001	100
A1C	7.1 ± 1.2	6.9 ± 1.1	7.3 ± 1.3	7.4 ± 1.3	6.7 ± 1.2	6.5 ± 2.5	<0.0001	99.8
Diet/tablet/insulin	19/57/24	23/59/18	15/59/26	9/49/42	14/36/50	15/12/73	<0.0001	100
Hypertension*	61	52	68	85	92	79	<0.0001	99.5
Systolic blood pressure (mmHg)	130 ± 17	127 ± 15	133 ± 16	137 ± 19	139 ± 22	139 ± 16	<0.0001	99.3
Diastolic blood pressure (mmHg)	75 ± 11	75 ± 10	76 ± 11	76 ± 12	74 ± 12	75 ± 10	<0.0001	99.3
Serum creatinine (μmol/l)	80 ± 66	66 ± 16	69 ± 19	106 ± 40	301 ± 120	770 ± 179	<0.0001	92.1
Glomerular filtration rate (ml/min per 1.73 m <sup>2</sup> )	66.6 ± 18.2	71.1 ± 13.5	67.8 ± 15.5	50.4 ± 19.8	17.0 ± 6.9	5.9 ± 1.6	<0.0001	92.1
Glomerular filtration rate <60 (%)	11	3	7	54	100	100	<0.0001	92.1
Antihypertensive agents usage (0/1/2/3)	49/26/16/9	57/25/13/5	44/30/18/8	24/25/28/23	16/17/28/39	29/24/18/29	<0.0001	100
ARB or ACE inhibitor	2,964 (33)	1,452 (28)	986 (35)	380 (58)	133 (55)	13 (38)	<0.0001	
CCB	3,044 (34)	1,391 (27)	1,114 (40)	356 (54)	166 (69)	17 (50)	<0.0001	
β-blockers	504 (6)	220 (4)	194 (7)	56 (9)	30 (12)	4 (12)	<0.0001	
α-blockers	254 (3)	105 (2)	73 (3)	37 (6)	35 (15)	4 (12)	<0.0001	
Diuretics	819 (9)	351 (7)	193 (7)	154 (23)	106 (44)	15 (44)	<0.0001	
Triglycerides (mmol/l)	1.68 ± 1.33	1.57 ± 2.23	1.75 ± 1.59	2.07 ± 1.68	1.93 ± 1.16	2.16 ± 2.22	<0.0001	94.4
Total cholesterol (mmol/l)	5.1 ± 1.0	5.1 ± 0.8	5.1 ± 0.9	5.3 ± 1.1	5.1 ± 1.4	4.7 ± 1.2	<0.0001	89.8
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.2 ± 0.4	1.4 ± 0.5	<0.0001	88.5
Antihyperlipidemic agents (0/1/2)	66/32/2	68/3/1	65/33/2	63/34/3	53/44/3	62/38/0	<0.0001	100
Use of aspirin	11	8	13	18	19	18	<0.0001	100
Attainment of goals								
A1C <6.5%	31	35	26	21	42	62	<0.0001	
Blood pressure <130/80 mmHg	42	48	34	29	27	24	<0.0001	
Total cholesterol <5.2 mmol/l	55	55	55	49	60	67	0.029	
Triglycerides <1.68 mmol/l	63	67	64	50	50	63	<0.0001	
HDL cholesterol >1.03 mmol/l	83	85	84	75	63	65	<0.0001	

Data are n (%), means ± SD, or percentages unless otherwise indicated. \*Hypertension was defined as systolic blood pressure ≥140, diastolic blood pressure ≥90, or taking antihypertensives. Glomerular filtration rate 186 × (Scr + 0.2)<sup>-1.154</sup> × age<sup>-0.203</sup> × 0.742 (if female) × 0.881 (by the Modification of Diet in Renal Disease method refitted for Japanese patients). CCB, calcium channel blocker.

**CONCLUSIONS**— This nation-wide large-population study revealed that the prevalence of microalbuminuria in Japanese type 2 diabetic patients was 32%. The DEMAND (Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes) study stated that the overall global prevalence of microalbuminuria among 24,151 patients with type 2 diabetes was 39% (5), and the MAP (MicroAlbuminuria Prevalence) study reported the prevalence at 40% among 5,549 Asian patients (4). These findings indicate that microalbuminuria is common.

Our study is the second largest in terms of the number of subjects investigated and, furthermore, achieved high data availability, with 60% of multiple quantitative measurements for UAE, while other large-population studies performed single measurements by dipstick with 20–40% of data-missing rates for A1C and blood pressure levels (4,5). The mean levels of major risk for microalbuminuria were low in our study. However, the prevalence of microalbuminuria in our subjects exceeded 45% at risk levels similar to those in the DEMAND and MAP studies (systolic blood pressure 140 mmHg or A1C 7.5%) [data not shown]. This indicates that the Japanese type 2 diabetic population may be susceptible to developing microalbuminuria. More strict control of blood pressure and A1C is needed for reducing UAE, for instance, by incorporating more ARBs/ACE inhibitors and diuretics, which were prescribed, respectively, to only 33 and 9% of Japanese patients, rates lower than those for Caucasians (58 and 29%, respectively) (5).

About 40% of patients had no ACR measurements regardless of the recommendation. There was a variation among the clinics in the frequency of ACR measurements, while the distribution of nephropathy stages did not differ. Alternatively, we should acknowledge that a few patients did not undergo UAE determination in daily practice. Such investigations have never been done, but this might be the case in other Asian or Western countries. The actual prevalence of microalbuminuria is considered even higher if we take nonattending diabetic patients into account.

Intervention studies with ARB (18), pioglitazone (19,20), and acarbose (20–22) have yielded a reduction not only in UAE but also in cardiovascular morbidity. The facts would emphasize the impor-

tance of multifactorial treatment for modifiable risks aiming at reducing UAE and associated risks.

#### References

- Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham study. *JAMA* 241:2035–2038, 1979
- Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141–1147, 1991
- Bennett P, Lee ET, Lu M, Keen H, Fuller JH: Increased urinary albumin excretion and its associations in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):S37–S45, 2001
- Wu AYT, Kong NCT, de Leon FA, Pan CY, Tai TY, Yeung VT, Yoo SJ, Rouillon A, Weir MR: An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: the MicroAlbuminuria Prevalence (MAP) Study. *Diabetologia* 48: 17–26, 2005
- Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG, DEMAND investigators: Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. *Kidney Int* 69:2057–2063, 2006
- Varghese A, Deepa R, Rema M, Mohan V: Prevalence of microalbuminuria in type 2 diabetes mellitus at a diabetes center in southern India. *Postgrad Med J* 77:399–402, 2001
- Jones CA, Francis ME, Eberhardt MS, Chavers B, Coresh J, Engelgau M, Kusek JW, Byrd-Holt D, Narayan KM, Herman WH, Jones CP, Salive M, Agodoa LY: Microalbuminuria in the US population: third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 39:445–459, 2002
- Mather HM, Chaturvedi N, Kehely AM: Comparison of prevalence and risk factors for microalbuminuria in South Asians and Europeans with type 2 diabetes mellitus. *Diabet Med* 15:672–677, 1998
- Metcalf PA, Baker JR, Scragg RKR, Dryson E, Scott AJ, Wild CJ: Microalbuminuria in a middle-aged workforce. *Diabetes Care* 16:1485–1493, 1993
- Nelson RG, Kunzelman CL, Pettitt DJ, Saad MF, Bennett PH, Knowler WC: Albuminuria in type 2 diabetes mellitus and impaired glucose tolerance in Pima Indians. *Diabetologia* 32:870–876, 1989
- Collins VR, Dowse GK, Finch CF, Zimmet PZ, Linnane AW: Prevalence and risk factors for micro- and macroalbuminuria in diabetic subjects and entire population of Nauru. *Diabetes* 38:1602–1610, 1989
- Gall MA, Rossing P, Skott P, Damsbo P, Vaag A, Bech K, Dejgaard A, Lauritzen M, Lauritzen E, Hougaard P, et al.: Prevalence of micro- and macroalbuminuria, arterial hypertension, retinopathy and large vessel disease in European type 2 (non-insulin dependent) diabetic patients. *Diabetologia* 34:655–661, 1991
- Gatling W, Knight C, Mullee MA, Hill RD: Microalbuminuria in diabetes: a population study of the prevalence and an assessment of three screening tests. *Diabet Med* 5:343–347, 1987
- Mogensen CE, Vestbo E, Poulsen PL, Christiansen C, Damsgaard EM, Eiskjær H, Frøland A, Hansen KW, Nielsen S, Pedersen MM: Microalbuminuria and potential confounders: a review and some observations on variability of urinary albumin excretion. *Diabetes Care* 18:572–581, 1995
- Kobayashi M, Yamazaki K, Hirao K, Oishi M, Kanatsuka A, Yamauchi M, Takagi M, Kawai K; Japan Diabetes Clinical Data Management Study Group: The status of diabetes control and antidiabetic drug therapy in Japan—a cross-sectional survey of 17,000 patients with diabetes mellitus (JDDM 1). *Diabetes Res Clin Pract* 73: 198–204, 2006
- Guideline Committee of the Japan Diabetes Society: *Japan Diabetes Society Guidelines for the Management of Diabetes Based on Scientific Evidences*. Tokyo, Japan Diabetes Society, 2004
- The Committee of Japan Diabetes Society for the Diagnostic Criteria of Diabetes Mellitus: report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus. *J Jpn Diabetes Soc* 42:385–404, 1999
- de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 110:921–927, 2004
- Yokoyama H, Katakami N, Yamasaki Y: Recent advances of intervention to inhibit progression of carotid intima-media thickness in patients with type 2 diabetes mellitus. *Stroke* 37:2420–2427, 2006
- Yokoyama H, Kuramitsu M, Yokota Y, Tada J, Kamikawa F, Kanno S, Matsushima M: Effect of combination therapy with pioglitazone and acarbose on the progression of early atherosclerosis in patients with type 2 diabetes. *J Jpn Diabetes Soc* 49:197–204, 2006
- Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen

L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; Proactive Investigators: Secondary prevention of

macrovascular events in patients with type 2 diabetes in the Proactive Study (Prospective Pioglitazone Clinical Trial in Macrovascular Events): a randomised controlled trial. *Lancet* 366:1279–1289, 2005

22. Hanefeld M, Cagaty M, Petrowitsch T, Neuser D, Petzinna D, Rupp M: Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 25: 10–16, 2004